Towards the ideal antiepileptic drug

Symposium highlights
EPILEPSY SOCIETY OF AUSTRALIA
Annual Scientific Meeting

Randomised controlled trials in epilepsy

Deficiencies of currently available anti-epileptic medications

Assessing potential AEDs: the role of animal models of epilepsy

Using current AEDs effectively
Drs Merritt and Putnam

The Merritt-Putnam Symposium is named in honour of H Houston Merritt, a neurologist, and Tracy J Putnam, a neurosurgeon, whose collaborative research into anticonvulsive drugs during the 1930s resulted in the discovery of phenytoin.

The story began when work with barbiturates led Drs Merritt and Putnam to question the conventional wisdom that antiepileptic activity could not be obtained without sedation, and to look instead at molecules containing a phenyl radical. The pharmaceutical company Parke Davis provided the researchers with 19 such compounds, one of which was diphenylhydantoin, a very promising anticonvulsant. Clinical trials followed, and there was soon no doubt that the new agent, now dubbed phenytoin, was a valuable addition to the armamentarium of physicians treating epilepsy.

Since 1981, the US Merritt-Putnam Symposium has become established as a highly regarded forum for the communication of advances in epilepsy research. With the support of Parke Davis initially, and proudly continued by Pfizer, the International Symposium has built on that success in order to help physicians worldwide keep up with the rapid pace of change in the field including the development of new AEDs.

The Merritt-Putnam Symposium has been an important part of the Epilepsy Society of Australia’s annual scientific programme since 1996 and is also supported by Pfizer.

### Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>Carbamazepine</td>
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<td>Felbamate</td>
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<td>Gabapentin</td>
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<td>Phenobarbitone</td>
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<td>Phenytoin</td>
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<td>Topiramate</td>
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<td>Valproate</td>
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<td>Vigabatrin</td>
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The perfect anti-epileptic drug (AED) would be well tolerated, safe, and available in both once-daily oral and parenteral formulations. Its administration would not only provide total seizure control but also arrest the epileptic process. Drug-related adverse events (AEs), if any, would be minimal, and there would be no potential for permanent damage, interaction with other agents, or teratogenicity.

Finally, the ideal AED would be free of any risk of addiction, dependence, and abuse – all this, of course, at minimal cost. Not only do currently available AEDs fall short of that ideal, but there are often faults and inconsistencies in how they are tested, regulated, and used. Advances have clearly been made, and continue to be made, but until the perfect drug is developed, the management of epilepsy will depend largely on the epilepsy syndrome under treatment in an individual patient.

Factors to consider in female patients include the effect of the treatment on fertility, sexual function, pregnancy, and the risk of birth defects. Reproductive function is also a concern for men. Pharmacokinetic issues arise for children and, at the other end of the scale, older people are often frail, have declining renal function, and are more likely to be receiving multiple agents for comorbid conditions. Because age-related renal impairment makes drug-drug interactions more likely, AEDs with a low propensity to interact – including GBP – (see abbreviations used on page 2) are of particular value in older people. Other populations with special needs include disabled patients (for whom compliance may be a problem), people with psychiatric and cognitive conditions, and those suffering from multiple disorders at any age.

Given these difficulties in targeting, and the multitude of clinical, pharmacokinetic and practical issues to consider, it is hard to envisage any single AED achieving total seizure freedom with uniform effectiveness. Furthermore, despite the claims made for certain treatments, there is no clear evidence that any AED is able to cure epilepsy. It can be argued that a reasonably consistent tendency for treatment to be associated with possible or probable cure has been established, but in the absence of well-designed prospective studies it would be premature to conclude that currently available AEDs achieve anything more than seizure suppression. Having said that, higher rates of remission are reported among treated patients compared with those who are left untreated or given inadequate treatment.

Some commentators assert that prolonged lack of seizures following withdrawal of an AED amounts to neuroprotection – the main goal of treatment. However, others take the view that neuroprotection is an active process that occurs during therapy. Overall, the evidence suggests that neuroprotection requires more than simple seizure suppression (Figure). A number of AEDs have been investigated for potential neuroprotective properties. LTG has shown promise in experimental studies and may protect against brain damage following cardiac arrest. Some of TPM’s multiple mechanisms of

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**Figure. Neuroprotection is more than lack of seizure recurrence.**

- Symptomatic treatment vs Neuroprotection
- Analogy on molecular biology with other drugs
- Significance of gene expression
  - Parallel changes in other conditions e.g. cell death in non-neuronal diseases
- Ablation of symptoms
  - Cognitive normalisation
  - Electrical normalisation
  - Imaging normalisation
  - Wide application in other neurological areas and molecular biology
Deficiencies of currently available anti-epileptic drugs

action appear to be potentially neuroprotective, and the ability of TGB to prevent neuronal damage is currently under experimental investigation.

Perhaps the best supported claim for neuroprotection is that of VPA – the first-line AED in all forms of generalised epilepsy, whether primary or symptomatic. However, any advantage it has in that regard must be weighed against the disadvantage of systemic side-effects.

It is important to bear in mind that even a single seizure may have catastrophic consequences for the patient (Table). Although the mechanisms underlying seizure aggravation are poorly understood, there is clear evidence that AEDs differ in the likelihood that they will cause it. For example, PHT carries less risk than CBZ and VGB, but no drug (with the possible exception of VPA) is entirely free of it.

<table>
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<th>No driving for a time</th>
<th>Insecurity about control, risk of SUDEP</th>
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<td>Lifestyle restrictions</td>
<td>Employment limitations</td>
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<td>Seizure reduction thresholds such as 75% and 50% are useful for regulatory purposes, but have little clinical relevance</td>
<td>For individual patients, seizure freedom is the most important outcome</td>
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Table. Even a single seizure may be catastrophic

Some, but not all, new AEDs have pharmacokinetic advantages over conventional agents, including:

- linear kinetics
- absent or reduced enzyme induction
- lower potential for drug interactions
- less protein binding

The impact of serum level on efficacy has yet to be fully elucidated. Most AEDs are eliminated by the liver, and the newer ones generally appear to have shorter half-lives than CBZ or PHT. Some are not fully bioavailable, and variations are observed in protein binding, and active metabolite formation. No new AED has as narrow a therapeutic index as PHT.

Truly controlled release (CR) formulations of AEDs are a major advance, offering a more predictable total area under the curve (AUC) than that seen with standard formulations, and improved side-effect profiles as a result of lower peak concentrations.

Some AEDs, including GBP, are free of enzyme induction but in others – principally CBZ – it poses considerable problems. The degree of autoinduction is unpredictable, and interdose variations may amount to 88% of the total for both the parent drug and its epoxide metabolite. Clearance is subject to sex- and age-related differences. The numerous generic agents on the market are not necessarily totally equivalent in this regard and their use may destabilise the patient.

Concerns about abuse, escape and dependency relate mainly to the use of benzodiazepines. It can be argued that, along with seizures, the greatest burden of epilepsy is a lack of knowledge about the cognitive and behavioural effects of AEDs on the offspring of women treated during pregnancy.

A single major adverse event (AE) is enough to damage a drug, but many potentially serious side-effects have been overcome by experience. In particular, it is increasingly clear that treatment should be introduced slowly.

Delays in achieving progress are inevitable given that approximately 130,000 patients must be treated before rare AEs can be confidently excluded. Some take years to come to light; for example, the effect of VGB on the visual field has only been confirmed after 8 years of marketing.

Other potential pitfalls include undertargeting, and underdosing in clinical trials. GBP, for example, was investigated at doses of 600-1200 mg* daily, which are now recognised as being much too low.

Specific safety issues include differences in approach between different countries. Overstatement of interaction effects may occur (few are clinically significant, and some may even be beneficial). Nevertheless, important interactions have been less well emphasised, such as that between CBZ and the macrolide group.

Other considerations are the propensity of AEDs to cause weight-gain, and the fact that parenteral formulations may exist, without being made available. Inappropriate claims of class effects may have enormous consequences for drugs, by extrapolation of theoretical concerns; not based on acceptable evidence.

* The recommended maximum dose of GBP as an adjunctive therapy in partial epilepsy is 2400 mg/day.
Among the regulatory problems in this context are non-syndromic clinical trials, and differences of opinion about the ethics of using placebo controls. Disagreement may also arise about the potential value of a new compound, as has happened with clobazam.

Changes enabling and encouraging pharmacists to substitute generic AEDs for labelled brands are very regrettable and can be expected to result in destabilisation of patients.

For the future, there is a need to target specific epilepsy syndromes – a task that will be facilitated by the spectacular progress being made in genetics, much of it by Australian investigators. New animal models will also be required. However, as novel interventions are developed and introduced, physicians must always bear in mind the total assessment of a drug is dependent on the balance of efficacy versus its safety, both of which are essential to be fully evaluated and made known.

References
It will also necessary to include epileptic animals in the preclinical evaluation of both the antiepileptic properties and the AEs associated with potential new AEDs. Finally, the impact of genetic diversity on safety should be studied preclinically using outbred rat and mice strains.

Although the mechanisms of pharmacoresistance are as yet poorly understood, the following approaches can be expected to increase our knowledge: investigation of brain tissue from pharmacoresistant patients; genome profiling of pharmacoresistant individuals; and the use of \textit{in vitro} and \textit{in vivo} animal models of pharmacoresistant epilepsy.

Proposed explanations of what causes pharmacoresistance can be broadly categorised as genetic, disease-related, or drug-related. Recent work has focused in particular on overexpression of multidrug transporters in human epileptogenic tissue, principally the proteins PGP, MRP1 and MRP2. More work is necessary, but clinical inhibition of such molecules may be of use in the management of pharmacoresistant epilepsy.

Primary targets in the search for an AED with the potential to modify or prevent the disease are:
- ictogenesis (the initiation, amplification and propagation of seizures);
- epileptogenesis (the development of epilepsy, that is brain alterations that increase susceptibility to spontaneous recurrent seizures); and
- processes involved in progression to chronic epilepsy.

The Figure illustrates the steps that characterise the development and progression of epilepsy, including opportunities for pharmacological intervention.\footnote{Figure}{

In summary, animal models have a variety of roles in epilepsy research. Those involving reactive seizures in normal brains (the MES test) have been used to identify numerous clinically efficacious AEDs, but are inappropriate when the aim is to prevent or treat epilepsy, rather than to address the seizures alone. Models of chronic epilepsy, such as kindling, may be more useful in that respect, and in the development of drugs to treat pharmacoresistant epilepsy, but require validation.

References


\begin{figure}
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\caption{Figure. Steps in the development and progression of epilepsy, including opportunities for pharmacological intervention.}
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Randomised controlled trials (RCTs) are the least biased way yet devised of estimating a treatment effect. Assuming that the subject population is sufficiently large, and that the design and conduct of the study are of high enough quality, all the known (and unknown) prognostic factors will be evenly distributed between the groups, enabling any difference to be confidently attributed to the treatment.

Although RCTs are intended to detect benefit, they may also provide information about short-term tolerability and drug-related adverse events (AEs). However, they tell us nothing about rare but idiosyncratic reactions, such as the approximately 1:5000 risk of aplastic anaemia associated with felbamate. They are also too short to detect reliably chronic toxicity that develops over 5-10 years, and have too low an event rate to be sure of detecting teratogenicity.

Given the chronic nature of most neurological disorders, the inability of RCTs to determine long-term outcomes is a major problem. The lack of sensitivity regarding AEs means that they cannot be expected to provide a complete picture of overall risk-benefit.

Numerous issues may confound estimates of treatment effects in epilepsy. Many studies in epilepsy are of a ‘before and after’, essentially observational in nature. They are very vulnerable to confounding by regression to the mean. Physicians managing chronic conditions like epilepsy have a tendency to change treatment when the patient’s condition worsens. On average, the next period is likely to be better than that preceding the change, reflecting regression to the mean rather than a treatment effect. Randomisation with a control group offers the strongest protection against misinterpretation of this kind.

Although blinding is intended to eliminate observer bias, its effectiveness is often questionable. Other potential sources of major bias are patient exclusion and loss to follow-up, failure to adequately conceal information about randomisation, and inappropriate analysis of data by subgroup.

Traditionally, RCTs compare outcomes in terms of p values, which indicate the likelihood of an observation occurring by chance, but say nothing about the size of the treatment effect. A more informative approach from a clinical point of view is to provide an estimate of a ratio or difference for an outcome with appropriate confidence intervals.

RCTs can be conducted in a variety of ways. Most investigations in the field of epilepsy are industry-sponsored, short-term, placebo-controlled, add-on studies assessing primary outcomes with little clinical relevance. The aim is generally to obtain regulatory approval of an AED rather than to facilitate its use in everyday clinical practice.

Regulatory bodies are concerned mainly with statistically significant differences in efficacy and safety between the drug concerned and a placebo. Issues such as departure from clinical practice, and outcomes and differences of dubious clinical importance are of little interest to them.

Essentially, regulators require explanatory clinical trials that provide answers from very restricted clinical data however. There is more value in pragmatic trials that measure effectiveness rather than efficacy and also take account of factors such as tolerability and safety. Pragmatic trials are randomised, but often unblinded. The aim is to replicate everyday clinical practice as closely as possible, resulting in fewer exclusions, use clinically important outcomes, and intent to treat data analysis. Some pragmatic investigations examine policies rather than treatments.

Between the two extremes of pure explanatory and pure pragmatic trials lies a spectrum of hybrid protocols (Figure 1, over). The choice of which to adopt largely depends on the question...
being addressed. Explanatory trials are appropriate when proof of concept is required, and when elucidating possible mechanisms of treatment effects. Pragmatic trials focus on clinical practice in the round – often warts and all.

The literature concerning epilepsy management is relatively lacking in comparative studies, yet, as Bradford Hill put it nearly 40 years ago:

\[ \text{The essential medical question is how a new treatment compares with an old one; not whether the new treatment is better than nothing.} \]

That remark remains very relevant. Effective means of controlling seizures were first developed more than a century ago, and new drugs have continued to be introduced ever since. The greater the choice in terms of how and when to influence the epileptic process, however, the more important it is to try to ensure that the optimum regimen is used.

An AED superior in efficacy and tolerability to standard treatment would clearly become the new agent of choice. A drug with similar or equivalent efficacy to a standard, but a better tolerability profile, might become the first choice as long as there was no doubt about the efficacy finding. Importantly, failure to detect a difference in efficacy may simply reflect a lack of statistical power, and is not to be confused with equivalence.

In assessing equivalence it is necessary to consider the smallest clinically important difference in outcome that would influence the choice of one drug over another. The approach adopted in SANAD is to attempt to establish noninferiority for primary outcomes (95% CI contained within ±10% of the hazard ratio against the standard). About 70% of subjects are expected to achieve 1-year remission.

**Systematic Review and Meta-analysis**

The pace at which RCTs in epilepsy are being published makes it almost impossible for physicians to keep up-to-date with the literature. There is therefore a tendency to rely on reviews in order to reach conclusions. Unfortunately, however, the very rigorous mechanisms by which bias is eliminated in primary research do not necessarily apply to reviews – many of which are far from systematic. Strategies to improve their quality include systematic review and meta-analysis as exemplified by the work of the Cochrane Collaboration.

As Archie Cochrane, the founder, put it in 1971:

\[ \text{It is surely a great criticism of our profession that we have not organised a critical summary by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials.} \]
The Cochrane Library is undoubtedly the best source of RCTs. At the end of 2001, about 200 new papers on epilepsy were being added every 3 years, and the figure is now probably close to 200 every 2 years.

The reliability of evidence for effectiveness depends on how it is obtained. Figure 2 illustrates a hierarchy in which the least and most trustworthy sources are individual case reports and individual patient data meta-analysis, respectively.

Figure 3 shows aggregate data from add-on, placebo-controlled clinical trials involving a total of more than 5000 patients with partial epilepsy. Most of the AEDs assessed were clearly effective in terms of achieving a 50% reduction in seizures. No drug was convincingly superior to any other, but some, like GBP, were probably tested at close to the minimum effective dose.

Aggregate meta-analyses are the only way to compare AEDs as add-on at present, but their findings are indirect and difficult to interpret because of potential heterogeneity in the study populations included. Individual patient data reviews provide an alternative and more satisfactory approach from which to draw conclusions, but are very demanding and time-consuming to conduct.

In summary:
- RCTs have value
- Too few RCTs in epilepsy address clinically important questions and are of sufficient size and quality to guide practice
- Even coping with the literature as it stands is difficult
- There is a need to explore other means of assessing the long-term risks and benefits of different interventions

References

Figure 2. Hierarchy of evidence for effectiveness.

Figure 3. Placebo-controlled add-on studies in partial epilepsy. A summary of aggregate meta-analyses.
The armamentarium for physicians treating epilepsy contains a number of older AEDs that have become familiar since their introduction, in some instances many years ago. PHB, PRM and PHT were all at some time first-line drugs of choice in the treatment of epilepsy, but gave way to CBZ and VPA, the current preferences. The most widely used newer AEDs are LTG, GBP, TGB, and TPM (VGB was also used extensively until retinal toxicity was recognised).

Ideally, the choice of first AED would be a rational one made on the basis of knowledge about how the patient’s particular epilepsy is likely to respond to a particular drug. In the absence of complete knowledge, there appears to be a broad consensus that CBZ is the preferred treatment for partial epilepsies, as VPA is for generalised epilepsies.

Four Cochrane meta-analyses have compared CBZ with PHT, PHT with VPA, PHT with PHB, and CBZ with VPA. The first three detected virtually no differences, other than that when PHT was compared with PHB, the rate of drop out because of AEs was higher in the PHB arm.

The comparison of CBZ with VPA revealed no statistically significant differences in time to withdrawal or overall time to first seizure. Time to first partial seizure favoured CBZ, whereas when only generalised seizures were considered there was a trend towards VPA. Time to 12-month remission exhibited a trend in favour of CBZ that became significant when partial seizures alone were included in the analysis.

Interestingly, younger patients were found to benefit more from treatment with VPA than with CBZ, whereas the opposite was true among older individuals. The mechanism underlying this age difference is not clear, but it may reflect the fact that younger people are likely to present with idiopathic generalised syndromes, and older ones with cryptogenic or symptomatic focal epilepsies.

With regard to outcomes, the literature indicated that at 1 year, 40-60% of patients will have had no further seizures since the start of treatment; by 3 years, the figure drops to 30-50%. The rate of 1-year remission at 2 years is 60-80%, and the rate of 2-year remission at 5 years is 55-80%. Over time, there is a trend towards longer and longer remissions.

One review from the US reported that up to 70% of patients were well controlled on one AED, 15% achieved acceptable control with a 2- or 3-drug regimen, and the remaining 15% could not be controlled with pharmacotherapy. Surgical intervention was necessary in 5%.

When treating adults and adolescents, there is evidence to support the use of VPA in generalised epilepsy syndromes and CBZ (or, mainly in the US, PHT) in partial syndromes. From a practical point of view, physicians should bear in mind that people who present to emergency services with clusters of seizures are likely to have been given PHT already.

The long-term target of epilepsy treatment is clearly complete seizure freedom; however, the initial goal is an immediate cessation of seizures. When the patient has had relatively few seizures, or seizures with significant intervals between them, the question arises whether to administer an AED in a dose reported to be successful under similar circumstances, or to aim at a target therapeutic concentration.

Use of plasma drug levels has diminished recently, largely because the linear kinetics of newer drugs are thought to have made them unnecessary. A growing acceptance that there is no need to obtain plasma levels at all is regrettable, given their value in establishing targets for initial treatment, determining individual therapeutic concentrations, elucidating unanticipated events (which are often due to poor adherence), and checking for drug interactions, particularly with phenytoin and other older agents.

When the first AED fails due to intolerance or idiosyncratic AEs, it is appropriate to switch to an alternative agent with a different structure and mode of action. If lack of seizure control is the problem, the first step is to increase the dose to the maximum tolerable level. Thereafter, practices
The US approach is to switch to a second AED, then a third, or administer a combination regimen. The preferred strategy in Australia is to add a second AED immediately.

A recent audit conducted in Glasgow found that 47% of approximately 500 epilepsy patients had become seizure-free in response to the first AED, rising to 60% when the second drug was also included. Most of the rise could be accounted for by switches to a second medication because of intolerance. Only 11% of those switched for lack of efficacy became seizure-free.

Further analysis of total response to the first AED revealed success rates of 44% among patients with cryptogenic, or symptomatic epilepsy, and 58% when the disorder was idiopathic.

The investigators also found that patients who achieved seizure freedom with the first AED had been prescribed doses mainly within limited ranges: 70% of responders were taking CBZ 400-600 mg, 93% at a dose less than 800 mg; the figures for VPA were 64% at 600-1000 mg, and 91% below 1500 mg; with LTG they were 63% at 125-200 mg, and 94% below 300 mg.

Such findings need to be interpreted with caution but, taken at face value, they suggest that the likelihood of seizure freedom is small when AEDs are administered at higher doses but this must not stop us using higher doses when necessary. But they do raise the possibility that combination therapy might be introduced early (after a first adequate trial of AED), rather than alternative monotherapy.

No consensus has been reached on whether it is better to switch agents or combine them after a first failure. The results of an ongoing trial with LTG and VPA are expected to be of interest, although the study population may be too small to allow firm conclusions to be drawn.

In the absence of reliable data, it has been argued that dual therapy at moderate doses is likely to be better tolerated than high doses of monotherapy. A considerable body of evidence already indicates that AEDs may have complementary effects, and satisfactory rationales have been proposed to explain them. Many trials involving the newer AEDs show that add-on therapy is indeed effective.

Common sense dictates that AEDs used in combination should either have different mechanisms of action or work in the same way but still produce an additive effect (Table). PHT, CBZ, LTG and O CZ are essentially sodium channel modulators; VGB, TGB, and PHB affect the GABA chloride moiety; and VPA, TMP and GBP have multiple mechanisms of action. According to some authors, the best results are obtained by adding a sodium channel blocker to a drug with multiple mechanisms of action.

Figure 1 illustrates an algorithm for the management of partial epilepsy syndromes. Treatment starts with CBZ, switching to VPA if CBZ is not tolerated. If seizures continue it is appropriate to increase the dose and then, if necessary, administer both drugs together. Figure 2, over, shows an algorithm for generalised epilepsy syndromes, starting with VPA and switching to or adding LTG if not tolerated or ineffective respectively.

If combinations fail, many other dual therapy regimens are available, each with its own efficacy and safety profiles.
In conclusion:

- The first goal of epilepsy treatment is to stop further seizures – long-term remission comes later
- Setting target drug concentrations has merit
- The role of therapeutic drug monitoring requires review
- When seizures recur, it is appropriate to increase the dose of AED to tolerance or control
- Dual therapy may prove superior to substitution
- Newer AEDs will find their place in practice
- Agents able to prevent or reverse epileptogenesis are awaited

According to some authors, the best results are obtained by adding a sodium channel blocker to a drug with multiple mechanisms of action.

References


† If switching between brands is indicated, it is advised that appropriate monitoring of the patient’s clinical condition as well as that of serum drug levels are performed. According to the Schedule of Pharmaceutical Benefits, generic brands of AED products in Australia are considered bioequivalent to their branded counterparts.

The Merritt-Putnam symposium and subsequent highlights have been proudly sponsored by Pfizer Pty Limited, ABN 50 008 422 348, Pfizer Pharmaceuticals Group, 38-42 Wharf Road, West Ryde, NSW 2114.

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PBS Information: Authority required. Treatment of partial epileptic seizures which are not controlled satisfactory by other antiepileptic drugs.